

Intended for  
**Denka Performance Elastomer, LLC**

Document type  
**Report**

Date  
**January 31, 2019**

**INCORPORATION OF IN  
VITRO METABOLISM DATA  
AND PHYSIOLOGICALLY  
BASED PHARMACOKINETIC  
MODELING IN A RISK  
ASSESSMENT FOR  
CHLOROPRENE  
SUPPLEMENTAL  
MATERIALS – PBPK  
MODEL CODE**

## Contents

<b>Introduction</b>	<b>3</b>
<b>Model Files</b>	<b>4</b>
Source Code for Model (Chloroprene.model)	4
States file (states.R)	8
Forcing Function for Timing of Exposure (forfunc.r)	9
Initial Model Parameter Values (chloroprene_model_init.r)	10
<b>Parameter Files</b>	<b>13</b>
Female mouse (female_mouse.r)	13
Male Mouse (male_mouse.r)	14
Female Rat (female_rat.r)	15
Male Rat (male_rat.r)	16
Human (human.r)	17
<b>R Script Files for Building Model</b>	<b>18</b>
First Building of Model (firstbuildmodel.R)	18
Rebuilding Model (rebuildmodel.R)	19
<b>R Script Files for Running Model</b>	<b>20</b>
Mouse Invivo (mouse_invivo.R)	20
Female Mouse Dose Metric (fmouse_dose_metric.r)	22
Male Mouse Dose Metric (mmouse_dose_metric.r)	24
Female Rat Dose Metric (frat_dose_metric.R)	26
Male Rat Dose Metric (mrat_dose_metric.R)	28
Human Dose Metric (human_dose_metric.R)	30
Human Continuous (human_cont.R)	32
<b>Data files used by Model</b>	<b>34</b>
Mouse13.csv	34
Mouse32.csv	35
Mouse90.csv	36

## Introduction

The PBPK model code provided below requires an R interpreter in order to compile and execute the model. This software can be obtained from <https://cran.r-project.org>. If you need assistance with compiling and executing the PBPK model code, please contact Cynthia Van Landingham ([cvanlandingham@ramboll.com](mailto:cvanlandingham@ramboll.com); 318-398-2091) or Jerry Campbell ([jcampbell@ramboll.com](mailto:jcampbell@ramboll.com); 919-765-8022).

## Model Files

### Source Code for Model (Chloroprene.model)

#Chloroprene PBPK Model

States = {

AI ,  
AX ,  
AM ,  
AMLU ,  
AMK ,  
ALU ,  
AL ,  
AK ,  
AS ,  
AR ,  
AF ,  
};

Outputs = {

MASBAL ,  
CLU ,  
CL ,  
CK ,  
CS ,  
CR ,  
CF ,  
CVLUM ,  
ppm ,  
AMP ,  
AMPLU ,  
AMPK ,  
cvi ,  
qcbal ,  
vbal  
};

Inputs = {EXPPULSE};

#BODY WEIGHT (kg)

BW = 0.03 ; # Body weight (kg)

#SPECIAL FLOW RATES

QPC = 30. ; # Unscaled Alveolar Vent (L/h/kg<sup>0.75</sup>)

QCC = 30. ; # Unscaled Cardiac Output (L/h/kg<sup>0.75</sup>)

#FRACTIONAL BLOOD FLOWS TO TISSUES

QLC = 0.161 ; # Flow to Liver as % Cardiac Output (unitless)

QFC = 0.07 ; # Flow to Fat as % Cardiac Output (unitless)

QSC = 0.15 ; # Flow to Slow as % Cardiac Output (unitless)

QKC = 0.10 ; # Flow to Kidney as % Cardiac Output (unitless)

#FRACTIONAL VOLUMES OF TISSUES

VLC = 0.055 ; # Volume Liver as % Body Weight (unitless)

VLUC = 0.007 ; # Volume Lung as % Body Weight (unitless)

VFC = 0.05 ; # Volume Fat as % Body Weight (unitless)

VRC = 0.014 ; # Volume Rapid Perfused as % Body Weight (unitless)

VSC = 0.77 ; # Volume Slow Perfused as % Body Weight (unitless)

VKC = 0.014 ; # Volume Kidney as % Body Weight (unitless)

#PARTITION COEFFICIENTS PARENT

PL = 1.25 ; # Liver/Blood Partition Coefficient (unitless)  
 PLU = 2.38 ; # Lung/Blood Partition Coefficient (unitless)  
 PF = 17.3 ; # Fat/Blood Partition Coefficient (unitless)  
 PS = 0.58 ; # Slow/Blood Partition Coefficient (unitless)  
 PR = 1.76 ; # Rapid/Blood Partition Coefficient (unitless)  
 PB = 7.83 ; # Blood/Air Partition Coefficient (unitless)  
 PK = 1.76 ; # Kidney/Blood Partition Coefficient (unitless)

#KINETIC CONSTANTS

MW = 88.5 ; # Molecular weight (g/mol)  
 # Metabolism in Liver  
 VMAXC = 8.88 ; # Scaled VMax for Oxidative Pathway:Liver (mg/h/BW<sup>0.75</sup>)  
 KM = 0.08 ; # Km for Oxidative Pathway:Liver (mg/L)  
 # Metabolism in Lung  
 VMAXCLU = 0.11 ; # Scaled VMax for Oxidative Pathway:Lung (mg/h/BW<sup>0.75</sup>)  
 KMLU = 0.25 ; # Km for Oxidative Pathway:Lung (mg/L)  
 KFLUC = 0.0 ; # Pseudo-first order clearance in lung (Km unidentifiable) (L/hr/BW<sup>0.75</sup>)  
 # Metabolism in Kidney  
 VMAXCKid = 0.03 ; # Scaled VMax for Oxidative Pathway:Kidney (mg/h/BW<sup>0.75</sup>)  
 KMKD = 9.59 ; # Km for Oxidative Pathway :Kidney

#DOSING INFORMATION

TSTOP = 7.0 ; # Dosing stop time  
 CONC = 13.0 ; # Initial concentration (ppm)

Dynamics {

# Scaled parameters

QC = QCC\*pow(BW,0.75) ; #Cardiac output  
 QP = QPC\*pow(BW,0.75) ; #Alveolar ventilation  
 QL = QLC\*QC ; #Liver blood flow  
 QF = QFC\*QC ; #Fat blood flow  
 QS = QSC\*QC ; #Slowly-perf tissue blood flow  
 QK = QKC\*QC ; #Kidney tissue blood flow  
  
 QRC = 1-QLC-QKC-QFC-QSC ; #Rapidly Perfused tissues  
 QR = QRC\*QC ; #Rapidly-perf tissue blood flow  
  
 VL = VLC\*BW ; #Liver volume  
 VLU = VLUC\*BW ; #Lung volume  
 VF = VFC\*BW ; #Fat tissue volume  
 VS = VSC\*BW ; #Slowly-perfused tissue volume  
 VR = VRC\*BW ; #Richly-perfused tissue volume  
 VK = VKC\*BW ; #kidney tissue volume

ROBC = 1 - VLC - VLUC - VFC - VSC - VRC - VKC ; #Rest of body un-perfused tissue for Monte Carlo sims

# METABOLISM

VMAX = VMAXC\*pow(BW,0.75) ; #Maximum rate of metabolism-Liver (mg/hr/kg-BW)  
 VMAXLU = VMAXCLU\*pow(BW,0.75) ; #Maximum rate of metabolism-Lung (mg/hr/kg-BW)  
 KFLU = KFLUC\*BW ;  
 VMAXKD = VMAXCKid\*pow(BW,0.75) ; #Maximum rate of metabolism-Kidney (mg/hr/kg-BW)

# Exposure Control (mg/L)

CIX = CONC\*MW/24450 ;

$$CI = CIX * EXPPULSE ;$$

# Tissue Venous Concentrations (mg/L)

$$CVLU = ALU / (VLU * PLU) ;$$

$$CVL = AL / (VL * PL) ;$$

$$CVK = AK / (VK * PK) ;$$

$$CVS = AS / (VS * PS) ;$$

$$CVR = AR / (VR * PR) ;$$

$$CVF = AF / (VF * PF) ;$$

# Concentration in Pulmonary/Arterial and venous blood Compartments (mg/L)

$$CPU = (QP * CI + (QF * CVF + QL * CVL + QS * CVS + QR * CVR + QK * CVK)) / (QP / PB + QC) ;$$

$$CX = CPU / PB ;$$

$$CV = (QF * CVF + QL * CVL + QS * CVS + QR * CVR + QK * CVK) / QC ;$$

$$CPUM = CPU * 1000 / MW ;$$

$$RAI = QP * CI ;$$

$$dt(AI) = RAI ;$$

$$RAX = QP * CX ;$$

$$dt(AX) = RAX ;$$

# Amount metabolized in Liver (mg)

$$RAM = VMAX * CVL / (KM + CVL) ;$$

$$dt(AM) = RAM ;$$

# Amount metabolized in Lung (mg)

$$RAMLU = VMAXLU * CVLU / (KMLU + CVLU) + KFLU * CVLU ;$$

$$dt(AMLU) = RAMLU ;$$

# Amount metabolized in Kidney (mg)

$$RAMK = VMAXKD * CVK / (KMKD + CVK) ;$$

$$dt(AMK) = RAMK ;$$

# Amount in Lung Compartment (mg)

$$RALU = QC * (CPU - CVLU) - RAMLU ;$$

$$dt(ALU) = RALU ;$$

# Amount in Liver Compartment (mg)

$$RAL = QL * (CVLU - CVL) - RAM ;$$

$$dt(AL) = RAL ;$$

# Amount in Kidney Compartment (mg)

$$RAK = QK * (CVLU - CVK) - RAMK ;$$

$$dt(AK) = RAK ;$$

# Amount in Slowly Perfused Tissues (mg)

$$RAS = QS * (CVLU - CVS) ;$$

$$dt(AS) = RAS ;$$

# Amount in Rapidly Perfused Tissues (mg)

$$RAR = QR * (CVLU - CVR) ;$$

$$dt(AR) = RAR ;$$

# Amount in Fat Compartment (mg)

$$RAF = QF * (CVLU - CVF) ;$$

$$dt(AF) = RAF ;$$

```

} # End of Dynamics

CalcOutputs {
# Mass-balance
    MASBAL = AI - AX - (AL+AM+AMLU+ALU+AK+AMK+AS+AR+AF) ;
    #Tissue Concentrations (mg/L)
    CLU = ALU/VLU ;
    CL = AL/VL ;
    CK = AK/VK ;
    CS = AS/VS ;
    CR = AR/VR ;
    CF = AF/VF ;
#Concentrations for plots
    CVLUM = CVLU*1000/MW ; #(umol/L)
#Dose metrics
    ppm = CONC ;
    AMP = ((AM*1000/MW)/(VL*1000))/(TSTOP/24) ;
    AMPLU = ((AMLU*1000/MW)/(VLU*1000))/(TSTOP/24) ;
    AMPK = ((AMK*1000/MW)/(VK*1000))/(TSTOP/24) ;

    cvl = CVL ;

#Blood Flow balance
    qcbal = QC - QL - QF - QS - QK - QR ;
#Tissue Volume balance
    vbal = BW*(1-ROBC) - VL - VLU - VF - VS - VK - VR ;

} # End of CalcOutputs

End.

```

## States file (states.R)

#Initial state values

```
Y <- c(  
  AI = 0.0,  
  AX = 0.0,  
  AM = 0.0,  
  AMLU = 0.0,  
  AMK = 0.0,  
  ALU = 0.0,  
  AL = 0.0,  
  AK = 0.0,  
  AS = 0.0,  
  AR = 0.0,  
  AF = 0.0  
)
```

## Forcing Function for Timing of Exposure (forfunc.r)

```

#Exposure commands
#tlength --> Length of exposure in hours
#daysperwk --> days per week to expose (set to 5 if 5 exposures and 7 if everyday)
#numexp --> number of days to expose animals
ftime <- times
# Create a signal data frame to hold the vectors for all forcing functions.
# All vectors are initialised to zero
signal <- as.data.frame(list(ftime = ftime,
                            day = ftime/24,                #day of study
                            tofday=round(ftime%%24, digits = 3), #time of day (24 hour clock)
                            dofwk = round(((ftime/24)%%7), digits=3), #day of week 1 to 7
                            import1 = rep(0, length(ftime))    #Pulse for length of daily exposure
                            ))

#Inhalation exposure control (creates a square pulse for each time step of model)
signal$import1[signal$tofday >= dstart & signal$tofday < (dstart+dlength)] <- 1.0
signal$import1[signal$dofwk >= ddaysperwk] <- 0.0
signal$import1[signal$ftime > ddepend*24] <- 0.0
#####
#####
sigimp <- approxfun(signal$ftime, signal$import1, rule = 2)

Sigimp <- approx(signal$ftime, signal$import1, xout=ftime ,rule = 2)$y

forcings1 <- cbind(ftime, Sigimp)

forcings <- list(
  data.frame(forcings1)
)

forcout <- data.frame(forcings)

```

## Initial Model Parameter Values (chloroprene\_model\_init.r)

```
initParms <- function(newParms = NULL) {  
  parms <- c(  
    BW = 0.0,  
    QPC = 0.0,  
    QCC = 0.0,  
    QLC = 0.0,  
    QFC = 0.0,  
    QSC = 0.0,  
    QKC = 0.0,  
    VLC = 0.0,  
    VLUC = 0.0,  
    VFC = 0.0,  
    VRC = 0.0,  
    VSC = 0.0,  
    VKC = 0.0,  
    PL = 0.0,  
    PLU = 0.0,  
    PF = 0.0,  
    PS = 0.0,  
    PR = 0.0,  
    PB = 0.0,  
    PK = 0.0,  
    MW = 0.0,  
    VMAXC = 0.0,  
    KM = 0.0,  
    VMAXCLU = 0.0,  
    KMLU = 0.0,  
    KFLUC = 0.0,  
    VMAXCKid = 0.0,  
    KMKD = 0.0,  
    TSTOP = 0.0,  
    CONC = 0.0  
  )  
  
  parms <- within(as.list(parms), {  
    BW = 0.03;  
    QPC = 30.;  
    QCC = 30.;  
    QLC = 0.161;  
    QFC = 0.07;  
    QSC = 0.15;  
    QKC = 0.10;  
    VLC = 0.055;  
    VLUC = 0.007;  
    VFC = 0.05;  
    VRC = 0.014;  
    VSC = 0.77;  
    VKC = 0.014;  
    PL = 1.25;  
    PLU = 2.38;  
    PF = 17.3;  
    PS = 0.58;  
    PR = 1.76;  
    PB = 7.83;  
    PK = 1.76;  
  })  
}
```

```

MW = 88.5;
VMAXC = 8.88;
KM = 0.08;
VMAXCLU = 0.11;
KMLU = 0.25;
KFLUC = 0.0;
VMAXCKid = 0.03;
KMKD = 9.59;
TSTOP = 7.0;
CONC = 13.0;
})

if (!is.null(newParms)) {
  if (!all(names(newParms) %in% c(names(parms)))) {
    stop("illegal parameter name")
  }
}

if (!is.null(newParms))
  parms[names(newParms)] <- newParms
out <- .C("getParms", as.double(parms),
         out=double(length(parms)),
         as.integer(length(parms)))$out
names(out) <- names(parms)
out
}

Outputs <- c(
  "MASBAL",
  "CLU",
  "CL",
  "CK",
  "CS",
  "CR",
  "CF",
  "CVLUM",
  "ppm",
  "AMP",
  "AMPLU",
  "AMPK",
  "cvi",
  "qcbal",
  "vbal"
)

initStates <- function(parms, newStates = NULL) {
  Y <- c(
    AI = 0.0,
    AX = 0.0,
    AM = 0.0,
    AMLU = 0.0,
    AMK = 0.0,
    ALU = 0.0,
    AL = 0.0,
    AK = 0.0,
    AS = 0.0,
    AR = 0.0,
    AF = 0.0
  )
}

```

```
if (!is.null(newStates)) {  
  if (!all(names(newStates) %in% c(names(Y)))) {  
    stop("illegal state variable name in newStates")  
  }  Y[names(newStates)] <- newStates  
}  
Y  
}
```

## Parameter Files

### Female mouse (female\_mouse.r)

#Female mouse parameters (See Report for documentation of parameters)

parms <-c(

BW = 0.03 , # Body weight (kg)

QPC = 29.1 , # Unscaled Alveolar Vent (L/h/kg<sup>0.75</sup>)

QCC = 20.1 , # Unscaled Cardiac Output (L/h/kg<sup>0.75</sup>)

#FRACTIONAL BLOOD FLOWS TO TISSUES

QLC = 0.161 , # Flow to Liver as % Cardiac Output (unitless)

QFC = 0.07 , # Flow to Fat as % Cardiac Output (unitless)

QSC = 0.159 , # Flow to Slow as % Cardiac Output (unitless)

QKC = 0.09 , # Flow to Kidney as % Cardiac Output (unitless)

#FRACTIONAL VOLUMES OF TISSUES

VLC = 0.055 , # Volume Liver as % Body Weight (unitless)

VLUC = 0.0073 , # Volume Lung as % Body Weight (unitless)

VFC = 0.1 , # Volume Fat as % Body Weight (unitless)

VRC = 0.08098 , # Volume Rapid Perfused as % Body Weight (unitless)

VSC = 0.384 , # Volume Slow Perfused as % Body Weight (unitless)

VKC = 0.0167 , # Volume Kidney as % Body Weight (unitless)

#PARTITION COEFFICIENTS PARENT

PL = 1.26 , # Liver/Blood Partition Coefficient (unitless)

PLU = 2.38 , # Lung/Blood Partition Coefficient (unitless)

PF = 17.35 , # Fat/Blood Partition Coefficient (unitless)

PS = 0.59 , # Slow/Blood Partition Coefficient (unitless)

PR = 1.76 , # Rapid/Blood Partition Coefficient (unitless)

PB = 7.8 , # Blood/Air Partition Coefficient (unitless)

PK = 1.76 , # Kidney/Blood Partition Coefficient (unitless)

#KINETIC CONSTANTS

MW = 88.5 , # Molecular weight (g/mol)

#Revised Metabolism Constants based on Yoon report

# Metabolism in Liver

VMAXC = 8.8 , # Scaled VMax for Oxidative Pathway:Liver (mg/h/BW<sup>0.75</sup>)

KM = 0.08 , # Km for Oxidative Pathway:Liver (mg/L)

# Metabolism in Lung

VMAXCLU = 0.11 , # Scaled VMax for Oxidative Pathway:Lung (mg/h/BW<sup>0.75</sup>)

KMLU = 0.25 , # Km for Oxidative Pathway:Lung (mg/L)

KFLUC = 0.0 , # Pseudo-first order clearance in lung (L/h/BW<sup>0.75</sup>)

# Metabolism in Kidney

VMAXCKid = 0.03 , # Scaled VMax for Oxidative Pathway:Kidney (mg/h/BW<sup>0.75</sup>)

KMKD = 9.59 , # Km for Oxidative Pathway :Kidney (mg/L)

#DOSING INFORMATION

TSTOP = 7.0 ,

CONC = 0.0 # Initial concentration (ppm)

)

## Male Mouse (male\_mouse.r)

#Male mouse paramters (See Report for Documentation)

```

parms <-c(
  BW = 0.03 , # Body weight (kg)
  QPC = 29.1 , # Unscaled Alveolar Vent (L/h/kg^0.75)
  QCC = 20.0 , # Unscaled Cardiac Output (L/h/kg^0.75)

  #FRACTIONAL BLOOD FLOWS TO TISSUES
  QLC = 0.161 , # Flow to Liver as % Cardiac Output (unitless)
  QFC = 0.07 , # Flow to Fat as % Cardiac Output (unitless)
  QSC = 0.15 , # Flow to Slow as % Cardiac Output (unitless)
  QKC = 0.09 , # Flow to Kidney as % Cardiac Output (unitless)

  #FRACTIONAL VOLUMES OF TISSUES
  VLC = 0.055 , # Volume Liver as % Body Weight (unitless)
  VLUC = 0.007 , # Volume Lung as % Body Weight (unitless)
  VFC = 0.1 , # Volume Fat as % Body Weight (unitless)
  VRC = 0.08098 , # Volume Rapid Perfused as % Body Weight (unitless)
  VSC = 0.384 , # Volume Slow Perfused as % Body Weight (unitless)
  VKC = 0.0167 , # Volume Kidney as % Body Weight (unitless)

  #PARTITION COEFFICIENTS PARENT
  PL = 1.26 , # Liver/Blood Partition Coefficient (unitless)
  PLU = 2.38 , # Lung/Blood Partition Coefficient (unitless)
  PF = 17.35 , # Fat/Blood Partition Coefficient (unitless)
  PS = 0.59 , # Slow/Blood Partition Coefficient (unitless)
  PR = 1.76 , # Rapid/Blood Partition Coefficient (unitless)
  PB = 7.8 , # Blood/Air Partition Coefficient (unitless)
  PK = 1.76 , # Kidney/Blood Partition Coefficient (unitless)

  #KINETIC CONSTANTS
  MW = 88.5 , # Molecular weight (g/mol)

  # Metabolism in Liver
  VMAXC = 18.54 , # Scaled VMax for Oxidative Pathway:Liver (mg/h/BW^0.75)
  KM = 0.12 , # Km for Oxidative Pathway:Liver (mg/L)

  # Metabolism in Lung
  VMAXCLU = 0.6 , # Scaled VMax for Oxidative Pathway:Lung (mg/h/BW^0.75)
  KMLU = 0.2 , # Km for Oxidative Pathway:Lung (mg/L)
  KFLUC = 0.0 , # Pseudo-first order clearance in lung (L/hr/BW^0.75)

  # Metabolism in Kidney
  VMAXCKid = 0.078 , # Scaled VMax for Oxidative Pathway:Kidney (mg/h/BW^0.75)
  KMKD = 0.068 , # Km for Oxidative Pathway :Kidney (mg/L)

  #DOSING INFORMATION
  TSTOP = 7.0 ,
  CONC = 0.0 # Initial concentration (ppm)
)

```

## Female Rat (female\_rat.r)

#Female Fischer rat paramters (See Report for Documentation)

```

parms <-c(
  BW = 0.25 , # Body weight (kg)
  QPC = 22.4 , # Unscaled Alveolar Vent (L/h/kg^0.75)
  QCC = 18.7 , # Unscaled Cardiac Output (L/h/kg^0.75)

  #FRACTIONAL BLOOD FLOWS TO TISSUES
  QLC = 0.183 , # Flow to Liver as % Cardiac Output (unitless)
  QFC = 0.07 , # Flow to Fat as % Cardiac Output (unitless)
  QSC = 0.278 , # Flow to Slow as % Cardiac Output (unitless)
  QKC = 0.14 , # Flow to Kidney as % Cardiac Output (unitless)

  #FRACTIONAL VOLUMES OF TISSUES
  VLC = 0.0366 , # Volume Liver as % Body Weight (unitless)
  VLUC = 0.005 , # Volume Lung as % Body Weight (unitless)
  VFC = 0.1 , # Volume Fat as % Body Weight (unitless)
  VRC = 0.04644 , # Volume Rapid Perfused as % Body Weight (unitless)
  VSC = 0.4 , # Volume Slow Perfused as % Body Weight (unitless)
  VKC = 0.0073 , # Volume Kidney as % Body Weight (unitless)

  #PARTITION COEFFICIENTS PARENT
  PL = 1.58 , # Liver/Blood Partition Coefficient (unitless)
  PLU = 1.85 , # Lung/Blood Partition Coefficient (unitless)
  PF = 16.99 , # Fat/Blood Partition Coefficient (unitless)
  PS = 0.60 , # Slow/Blood Partition Coefficient (unitless)
  PR = 2.29 , # Rapid/Blood Partition Coefficient (unitless)
  PB = 7.3 , # Blood/Air Partition Coefficient (unitless)
  PK = 2.29 , # Kidney/Blood Partition Coefficient (unitless)

  #KINETIC CONSTANTS
  MW = 88.5 , # Molecular weight (g/mol)

  #Metabolism in Liver
  VMAXC = 9.37 , # Scaled VMax for Oxidative Pathway:Liver (mg/h/BW^0.75)
  KM = 0.09 , # Km for Oxidative Pathway:Liver (mg/L)

  #Metabolism in Lung
  VMAXCLU = 0.0 , # Scaled VMax for Oxidative Pathway:Lung (mg/h/BW^0.75)
  KMLU = 0.0611 , # Km for Oxidative Pathway:Lung (mg/L)
  KFLUC = 0.16 , # Pseudo-first order clearance in lung (L/hr/BW^0.75)

  #Metabolism in Kidney
  VMAXCKid = 0.018, # Scaled VMax for Oxidative Pathway:Kidney (mg/h/BW^0.75)
  KMKD = 0.053 , # Km for Oxidative Pathway :Kidney (mg/L)

  #DOSING INFORMATION
  TSTOP = 7.0 ,
  CONC = 0.0 # Initial concentration (ppm)
)

```

## Male Rat (male\_rat.r)

#Male Fischer rat paramters (See Report for Documentation)

parms <-c(

BW = 0.25 , # Body weight (kg)

QPC = 22.4 , # Unscaled Alveolar Vent (L/h/kg<sup>0.75</sup>)

QCC = 18.7 , # Unscaled Cardiac Output (L/h/kg<sup>0.75</sup>)

#FRACTIONAL BLOOD FLOWS TO TISSUES

QLC = 0.183 , # Flow to Liver as % Cardiac Output (unitless)

QFC = 0.07 , # Flow to Fat as % Cardiac Output (unitless)

QSC = 0.278 , # Flow to Slow as % Cardiac Output (unitless)

QKC = 0.14 , # Flow to Kidney as % Cardiac Output (unitless)

#FRACTIONAL VOLUMES OF TISSUES

VLC = 0.0366, # Volume Liver as % Body Weight (unitless)

VLUC = 0.005 , # Volume Lung as % Body Weight (unitless)

VFC = 0.1 , # Volume Fat as % Body Weight (unitless)

VRC = 0.04644 , # Volume Rapid Perfused as % Body Weight (unitless)

VSC = 0.4 , # Volume Slow Perfused as % Body Weight (unitless)

VKC = 0.0073 , # Volume Kidney as % Body Weight (unitless)

#PARTITION COEFFICIENTS PARENT

PL = 1.58 , # Liver/Blood Partition Coefficient (unitless)

PLU = 1.85 , # Lung/Blood Partition Coefficient (unitless)

PF = 16.99 , # Fat/Blood Partition Coefficient (unitless)

PS = 0.60 , # Slow/Blood Partition Coefficient (unitless)

PR = 2.29 , # Rapid/Blood Partition Coefficient (unitless)

PB = 7.3 , # Blood/Air Partition Coefficient (unitless)

PK = 2.29 , # Kidney/Blood Partition Coefficient (unitless)

#KINETIC CONSTANTS

MW = 88.5 , # Molecular weight (g/mol)

#Metabolism in Liver

VMAXC = 9.48 , # Scaled VMax for Oxidative Pathway:Liver (mg/h/BW<sup>0.75</sup>)

KM = 0.05 , # Km for Oxidative Pathway:Liver (mg/L)

#Metabolism in Lung

VMAXCLU = 0.0 , # Scaled VMax for Oxidative Pathway:Lung (mg/h/BW<sup>0.75</sup>)

KMLU = 0.0611 , # Km for Oxidative Pathway:Lung (mg/L)

KFLUC = 0.15 , # Pseudo-first order clearance in lung (L/hr/BW<sup>0.75</sup>)

#Metabolism in Kidney

VMAXCKid = 0.018 , # Scaled VMax for Oxidative Pathway:Kidney (mg/h/BW<sup>0.75</sup>)

KMKD = 0.067 , # Km for Oxidative Pathway :Kidney (mg/L)

#DOSING INFORMATION

TSTOP = 7.0 ,

CONC = 0.0 # Initial concentration (ppm)

)

## Human (human.r)

#Human paramters (See Model Parameters Spreadsheet for Documentation)

```

parms <-c(
BW = 70.0 ,      # Body weight (kg)
QPC = 27.75 ,   # Unscaled Alveolar Vent (L/h/kg^0.75)
QCC = 12.89 ,   # Unscaled Cardiac Output (L/h/kg^0.75)

#FRACTIONAL BLOOD FLOWS TO TISSUES
QLC = 0.227 ,   # Flow to Liver as % Cardiac Output (unitless)
QFC = 0.052 ,   # Flow to Fat as % Cardiac Output (unitless)
QSC = 0.191 ,   # Flow to Slow as % Cardiac Output (unitless)
QKC = 0.175 ,   # Flow to Kidney as % Cardiac Output (unitless)

#FRACTIONAL VOLUMES OF TISSUES
VLC = 0.0257 ,  # Volume Liver as % Body Weight (unitless)
VLUC = 0.0076 , # Volume Lung as % Body Weight (unitless)
VFC = 0.27 ,    # Volume Fat as % Body Weight (unitless)
VRC = 0.0533 ,  # Volume Rapid Perfused as % Body Weight (unitless)
VSC = 0.4 ,     # Volume Slow Perfused as % Body Weight (unitless)
VKC = 0.0044 ,  # Volume Kidney as % Body Weight (unitless)

#PARTITION COEFFICIENT PARENT
PL = 2.37 ,     # Liver/Blood Partition Coefficient (unitless)
PLU = 2.94 ,    # Lung/Blood Partition Coefficient (unitless)
PF = 28.65 ,    # Fat/Blood Partition Coefficient (unitless)
PS = 1.00 ,     # Slow/Blood Partition Coefficient (unitless)
PR = 2.67 ,     # Rapid/Blood Partition Coefficient (unitless)
PB = 4.5 ,      # Blood/Air Partition Coefficient (unitless)
PK = 2.67 ,     # Kidney/Blood Partition Coefficient (unitless)

#KINETIC CONSTANTS
MW = 88.5 ,     # Molecular weight (g/mol)

#Metabolism in Liver
VMAXC = 20.4 ,  # Scaled VMax for Oxidative Pathway:Liver (mg/h/BW^0.75)
KM = 0.04 ,    # Km for Oxidative Pathway:Liver (mg/L)

#Metabolism in Lung
VMAXCLU = 0.0 , # Scaled VMax for Oxidative Pathway:Lung (mg/h/BW^0.75)
KMLU = 0.0885 , # Km for Oxidative Pathway:Lung (mg/L)
KFLUC = 0.05 , # Pseudo-first order clearance in lung (L/hr/BW^0.75)

#Metabolism in Kidney
VMAXCKid = 0.0 , # Scaled VMax for Oxidative Pathway:Kidney (mg/h/BW^0.75)
KMKD = 0.0885 , # Km for Oxidative Pathway :Kidney (mg/L)

#DOSING INFORMATION
TSTOP = 7.0 ,
CONC = 0.0 # Initial concentration (ppm)
)

```

## R Script Files for Building Model

### First Building of Model (firstbuildmodel.R)

```
setwd(dirname(parent.frame(2)$ofile))

# set the name of your model
mName <- "chloroprene.model"

#command to unload dll file (need if rebuilding dll file)
#dyn.unload(paste0(mPath,mName,.Platform$dynlib.ext))

system(paste("../mod/mod.exe -R ", mName, " ", mName, ".c", sep = ""))

system(paste0("R CMD SHLIB ", mName, ".c", sep = ""))
```

## Rebuilding Model (rebuildmodel.R)

```
setwd(dirname(parent.frame(2)$ofile))

# set the name of your model
mName <- "chloroprene.model"

#Remove old model files before building model
#ensures files are reset with changes in model
file.remove(paste(mName, ".c", sep = ""))
file.remove(paste(mName, ".o", sep = ""))
file.remove(paste(mName, ".dll", sep = ""))
file.remove(paste(mName, "_inits.R", sep = ""))

#command to unload dll file (need if rebuilding dll file)
#dyn.unload(paste0(mPath,mName,.Platform$dynlib.ext))

system(paste("../mod/mod.exe -R ", mName, " ", mName, ".c", sep = ""))

system(paste0("R CMD SHLIB ", mName, ".c", sep = ""))
```

## R Script Files for Running Model

### Mouse Invivo (mouse\_invivo.R)

```
# Simulates the 15 day mouse exposure study
# Data collected during and after exposure on 1st day
# and at end of exposure on day 5 and 15 (1 day nose-only)

#set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))
# load libraries needed to run scenario
library(deSolve)

# Model path and name
mName <- "chloroprene.model"

#load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#load the states files
#source(paste0(mPath,"states.R"))

#load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 443.0
times <- seq(tstart, tstop , by=0.01)

# Physiological parameters path

#load the parameters
source('./params/Male_Mouse.R')
source('./states.R')

# timing variables for forcing functions
dstart <- tstart
dlength <- 6 #hours per day to expose
ddaysperwk <- 5 #days of week to expose
dexpnd <- 19 #days of exposure
parms["TSTOP"] <- tstop

# Source forcing functions
# this loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<- 12.3

parms <- initParms(parms)
Y <- initState()

# Run ODE
print(system.time(
  out <- ode(Y, times, func = "derivs", parms = parms, method="vode",
    dllname = mName, initforc="initforc", forcings=forcings,
    initfunc = "initmod", nout = length(Outputs),
    outnames = Outputs)
```

```

))

out1 <- as.data.frame(out,stringsAsFactors = F)

#Scenario Specific Exposure
parms["CONC"]<- 32.0

parms <- initParms(parms)
Y <- initState()

# Run ODE
print(system.time(
  out <- ode(Y, times, func = "derivs", parms = parms, method="vode",
    dllname = mName, initforc="initforc", forcings=forcings,
    initfunc = "initmod", nout = length(Outputs),
    outnames = Outputs)
))

out2 <- as.data.frame(out,stringsAsFactors = F)

#Scenario Specific Exposure
parms["CONC"]<- 90.0

parms <- initParms(parms)
Y <- initState()

# Run ODE
print(system.time(
  out <- ode(Y, times, func = "derivs", parms = parms, method="vode",
    dllname = mName, initforc="initforc", forcings=forcings,
    initfunc = "initmod", nout = length(Outputs),
    outnames = Outputs)
))

out3 <- as.data.frame(out,stringsAsFactors = F)
#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))

## Read the dataset to be plotted
dataset1 <- read.csv("mouse13.csv",header = T,stringsAsFactors = F, skip=1)
dataset2 <- read.csv("mouse32.csv",header = T,stringsAsFactors = F, skip=1)
dataset3 <- read.csv("mouse90.csv",header = T,stringsAsFactors = F, skip=1)

plot(out1$time,out1$CVLUM, type = 'l', col='red',lwd = 2,
  xlab="TIME",ylab = expression(mu*"M"), main='Mouse In Vivo Study 1 Day',
  xlim=c(0.0,7.0), ylim=c(0.0,15.0))
points(out2$CVLUM~out2$time,type = 'l,col='blue', lwd=2)
points(out3$CVLUM~out3$time,type = 'l,col='orange', lwd=2)
points(dataset1$time,dataset1$cart,type = 'p',col='red', pch=21, bg='red')
points(dataset2$time,dataset2$cart,type = 'p',col='blue', pch=21, bg='blue')
points(dataset3$time,dataset3$cart,type = 'p',col='orange', pch=21, bg='orange')
plot(out1$time,out1$CVLUM, type = 'l', col='red',lwd = 2,
  xlab="TIME",ylab = expression(mu*"M"), main='Mouse In Vivo Study 3 Week',
  xlim=c(0.0,443.0), ylim=c(0.0,15.0))
points(out2$CVLUM~out2$time,type = 'l,col='blue', lwd=2)
points(out3$CVLUM~out3$time,type = 'l,col='orange', lwd=2)
points(dataset1$time,dataset1$cart,type = 'p',col='red', pch=21, bg='red')
points(dataset2$time,dataset2$cart,type = 'p',col='blue', pch=21, bg='blue')
points(dataset3$time,dataset3$cart,type = 'p',col='orange', pch=21, bg='orange')

```

## Female Mouse Dose Metric (fmouse\_dose\_metric.r)

```

# Simulates female mouse for 2 weeks using mouse study protocol (6 hr/day 5 days/week)
# Uses metabolism constants from Clewell et al. 2019 report
#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))
# Load libraries needed to run scenario
library(deSolve)

# Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

#Physiological parameters path
#Load the parameters
source('./params/Female_Mouse.R')
source('./states.R')

#Timing variables for forcing functions
dstart <- tstart
dlength <- 6 #hours per day to expose
ddaysperwk <- 5 #days of week to expose
dexpnd <- 12 #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<- 12.3
ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
outlist <- list()
ppm2 <- list()

for(i in 1:nrow(cinh1)){

  parms["CONC"] <- cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10, rtol=1.0e-8,
             dllname = mName, initforc="initforc", forcings=forcings, initfunc = "initmod", nout =
length(Outputs),
             fcontrol=list(method="linear"), outnames = Outputs)

  }
}

```

```
  outlist[[i]] <- out[33601,]
}
frou1 <- data.frame(outlist)
dout <- data.frame(t(frou1), row.names=paste(1:3))
rou <- cbind(dout[,c(21,22,23,24)])

"Female Mouse Dose Metric"
rou

#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

## Male Mouse Dose Metric (mmouse\_dose\_metric.r)

```
# Simulates male mouse for 2 weeks using mouse study protocol (6 hr/day 5 days/week)
# Uses metabolism constants from Clewell et al. 2019 report

#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))
# Load libraries needed to run scenario
library(deSolve)

# Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

#Physiological parameters path
#Load the parameters
source('./params/Male_Mouse.R')
source('./states.R')

#Timing variables for forcing functions
dstart <- tstart
dlength <- 6 #hours per day to expose
ddaysperwk <- 5 #days of week to expose
dexpnd <- 12 #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<- 12.3
ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
outlist <- list()
ppm2 <- list()

for(i in 1:nrow(cinh1)){

  parms["CONC"] <- cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10, rtol=1.0e-8,
      dllname = mName, initforc="initforc", forcings=forcings, initfunc = "initmod", nout =
length(Outputs),
      fcontrol=list(method="linear"), outnames = Outputs)
```

```
}  
  outlist[[i]] <- out[33601,]  
}  
frou1 <- data.frame(outlist)  
dout <- data.frame(t(frou1), row.names=paste(1:3))  
rou <- cbind(dout[,c(21,22,23,24)])  
  
"Male Mouse Dose Metric"  
rou  
  
#load the model dll  
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

## Female Rat Dose Metric (frat\_dose\_metric.R)

```

# Simulates female rat for 2 weeks using rat study protocol (6 hr/day 5 days/week)
# Uses metabolism constants from Clewell et al. 2019 report
#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))
# Load libraries needed to run scenario
library(deSolve)

# Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

#Physiological parameters path
#Load the parameters
source('./params/Female_Rat.R')
source('./states.R')

#Timing variables for forcing functions
dstart <- tstart
dlength <- 6 #hours per day to expose
ddaysperwk <- 5 #days of week to expose
dexpnd <- 12 #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<- 12.3
ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
outlist <- list()
ppm2 <- list()

for(i in 1:nrow(cinh1)){

  parms["CONC"] <- cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10, rtol=1.0e-8,
              dllname = mName, initforc="initforc", forcings=forcings, initfunc = "initmod", nout =
length(Outputs),
              fcontrol=list(method="linear"), outnames = Outputs)

  }
}

```

```
  outlist[[i]] <- out[33601,]
}
frou1 <- data.frame(outlist)
dout <- data.frame(t(frou1), row.names=paste(1:3))
rou <- cbind(dout[,c(21,22,23,24)])

"Female Rat Dose Metric"
rou

#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

## Male Rat Dose Metric (mrat\_dose\_metric.R)

```

# Simulates male rat for 2 weeks using rat study protocol (6 hr/day 5 days/week)
# Uses metabolism constants from Clewell et al. 2019 report
#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))
# Load libraries needed to run scenario
library(deSolve)

# Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

#Physiological parameters path
#Load the parameters
source('./params/Male_Rat.R')
source('./states.R')

#Timing variables for forcing functions
dstart <- tstart
dlength <- 6 #hours per day to expose
ddaysperwk <- 5 #days of week to expose
dexpnd <- 12 #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<- 12.3
ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
outlist <- list()
ppm2 <- list()

for(i in 1:nrow(cinh1)){

  parms["CONC"] <- cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10, rtol=1.0e-8,
             dllname = mName, initforc="initforc", forcings=forcings, initfunc = "initmod", nout =
length(Outputs),
             fcontrol=list(method="linear"), outnames = Outputs)

  }
}

```

```
  outlist[[i]] <- out[33601,]
}
frou1 <- data.frame(outlist)
dout <- data.frame(t(frou1), row.names=paste(1:3))
rou <- cbind(dout[,c(21,22,23,24)])

"Male Rat Dose Metric"
rou

#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

## Human Dose Metric (human\_dose\_metric.R)

```

#Simulates human for 2 weeks using mouse study protocol (6 hr/day 5 days/week)
#Uses metabolism constants from Clewell et al. 2019 report

#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))
#Load libraries needed to run scenario
library(deSolve)

#Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336
times <- seq(tstart, tstop , by=0.01)

#Physiological parameters path
#Load the parameters
source('./params/Human.R') #Revised parameters from June 27 2018 update
source('./states.R')
#Timing variables for forcing functions
dstart <- tstart
dlength <- 6 #hours per day to expose
ddaysperwk <- 5 #days of week to expose
dexpnd <- 12 #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

#Scenario Specific Exposure
parms["CONC"]<- 12.3

ppm <- c(12.3, 32.0, 80.0)
cinh1 <- data.frame(ppm)
cinh <- lapply(cinh1, as.numeric)
outlist <- list()
ppm2 <- list()

for(i in 1:nrow(cinh1)){

  parms["CONC"] <- cinh1[i,]

  {

    out <-ode(Y, times, func = "derivs", parms = parms, method="vode",atol=1.0e-10, rtol=1.0e-8,
      dllname = mName, initforc="initforc", forcings=forcings, initfunc = "initmod", nout =
length(Outputs),
      fcontrol=list(method="linear"), outnames = Outputs)
  }
}

```

```
}  
  outlist[[i]] <- out[33601,]  
}  
frou1 <- data.frame(outlist)  
dout <- data.frame(t(frou1), row.names=paste(1:3))  
rou <- cbind(dout[,c(21,22,23,24)])  
  
"Human Dose Metric"  
rou  
#load the model dll  
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

## Human Continuous (human\_cont.R)

```

# Simulates human continuous exposure to 1 ppb and 1 ug/m3 for 2 weeks
#Uses metabolism constants from Clewell et al. 2019 report

#Set the working directory to where you downloaded the scripts
setwd(dirname(parent.frame(2)$ofile))
#Load libraries needed to run scenario
library(deSolve)

#Model path and name
mName <- "chloroprene.model"

#Load model inits file for the ode solver
source(paste0(mName,"_inits.R"))

#Load the model dll
dyn.load(paste0(mName,.Platform$dynlib.ext))

#Scenario specific values
tstart <- 0.0
tstop <- 336.0
times <- seq(tstart, tstop , by=0.01)

#Physiological parameters path

#Load the parameters
source('./params/Human.R')#Revised parameters from June 27 2018 update
source('./states.R')

#Timing variables for forcing functions
dstart <- tstart
dlength <- 24 #hours per day to expose
ddaysperwk <- 7 #days of week to expose
dexpnd <- 500 #days of exposure
parms["TSTOP"] <- tstop

#Source forcing functions
#This loads the function forcing() in the namespace
source("forfunc.R")

ppm <- 0.001

#Scenario Specific Exposure
parms["CONC"] <- ppm
out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10, rtol=1.0e-8,
        dllname = mName, initforc="initforc", forcings=forcings, initfunc = "initmod", nout =
length(Outputs),
        fcontrol=list(method="linear"), outnames = Outputs)

out1 <- data.frame(out[33601,])

frou1 <- data.frame(out1)
dout <- data.frame(t(frou1), row.names=paste(1))
zout <-data.frame(rbind("1ppb"))
rou <- cbind(zout, dout[,c(21,22,23,24)])
colnames(rou)<- c("Run", "Conc", "AMU", "AMPLU", "AMPK")

#1 ug/m3

```

```
ppm <- 0.00028

#Scenario Specific Exposure
parms["CONC"] <- ppm
  out <-ode(Y, times, func = "derivs", parms = parms, method="vode", atol=1.0e-10, rtol=1.0e-8,
    dllname = mName, initforc="initforc", forcings=forcings, initfunc = "initmod", nout =
length(Outputs),
  fcontrol=list(method="linear"), outnames = Outputs)

  out1 <- data.frame(out[33601,])
frou1 <- data.frame(out1)
dout <- data.frame(t(frou1), row.names=paste(1))
zout <-data.frame(rbind("1ug/m3"))
sout <- cbind(zout, dout[,c(21,22,23,24)])
colnames(sout)<- c("Run", "Conc", "AMU", "AMPLU", "AMPK")

"Human Continuous Exposure"
rou1
sout

#load the model dll
dyn.unload(paste0(mName,.Platform$dynlib.ext))
```

## Data files used by Model

### Mouse13.csv

#13 ppm mouse in vivo study - 15 day exposure (last day is nose-only),

time, cart

0.5,0.97

0.5,0.82

0.5,1.12

0.5,1.22

3,0.6

3,2.7

3,2.03

3,2.1

3,2.24

6,2.08

6,1.75

6,1.53

6,1.37

6,1.16

6.083,0.08

6.083,0.09

6.083,0.16

6.17,0.1

6.17,0.25

102,0.17

102,0.23

102,0.2

102,0.18

438,0.28

438,0.33

438,0.24

438,0.31

## Mouse32.csv

#32 ppm mouse in vivo study – 15 day exposure (last day is nose-only), time, cart

0.5,3  
0.5,2.27  
0.5,1.66  
0.5,2.08  
0.5,0.69  
3,3.94  
3,3.9  
3,1.52  
3,2.48  
3,1.68  
3,3.87  
6,2.26  
6,1.26  
6,4.18  
6,2.06  
6.083,0.46  
6.083,0.41  
6.083,0.92  
6.083,0.52  
6.083,0.77  
6.17,0.28  
6.17,0.26  
6.17,0.1  
6.17,0.12  
6.17,0.13  
6.25,0.18  
6.25,0.31  
6.25,0.69  
6.25,0.16  
6.25,0.13  
102,2.32  
102,2.26  
102,1.15  
102,1.32  
102,0.88  
438,0.75  
438,2.08  
438,1.6  
438,1.12  
438,1.45

## Mouse90.csv

#32 ppm mouse in vivo study - 15 day exposure (last day is nose-only),

time, cart

0.5,5.92

0.5,4.86

0.5,4.82

0.5,8.26

0.5,7.69

3,7.42

3,12.95

3,7.18

3,3.46

3,5.62

6,9

6,6.46

6,7.63

6,8.79

6,8.12

6.083,1.39

6.083,3.01

6.083,1.62

6.083,0.92

6.083,1.59

6.17,0.66

6.17,1.46

6.17,0.67

6.17,0.88

6.17,0.93

6.25,0.94

6.25,0.63

6.25,0.57

6.25,0.64

6.25,0.58

102,3.73

102,5.48

102,4.09

102,3

102,6.43

438,4.44

438,3.64

438,2.76

438,3.41

438,1.96